Proposed Registration Decision PRD2012-34

d-Phenothrin

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Overview

Proposed Registration Decision for d-Phenothrin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Sumithrin Technical Grade (containing the active ingredient d-phenothrin) and eight domestic end-use products; four products containing d-phenothrin (Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies Weighing either 2.5-6 kg, 6-14 kg, 14-28 kg or greater than 28 kg), and four products containing a combination of the active ingredients s-methoprene and d-phenothrin (Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies Weighing either 2.5-6 kg, 6-14 kg, 14-28 kg or greater than 28 kg). All eight end-use products are spot-on products used to kill fleas and ticks and reduce biting by mosquitoes.

Although d-phenothrin has full registration in Canada, this application represents an expansion for a new use on companion animals (Use Site Category 24). Use on companion animals is already a registered use pattern for s-methoprene in Canada.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of d-phenothrin and eight Hartz end-use products.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on d-phenothrin, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on d-phenothrin, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is d-Phenothrin?

d-Phenothrin is a pyrethroid which stimulates the nerves to keep the sodium channels of insects open beyond their normal timing thresholds, causing paralysis and eventually death of the pest.

The combination active ingredient that is present in the Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies product line, s-methoprene, is an insect growth regulator that acts by mimicking the action of the juvenile hormone keeping the insect in an immature state which results in its eventual death.

Health Considerations

Can Approved Uses of d-Phenothrin Affect Human Health?

Products containing d-phenothrin are unlikely to affect your health when used according to label directions.

Potential exposure to d-phenothrin (Sumithrin Technical Grade) may occur when handling and applying the end-use products. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, the technical grade active ingredient d-phenothrin was slightly acutely toxic by the inhalation route of exposure; consequently, the hazard signal words "CAUTION-POISON" are required on the label. It was of low acute toxicity by the oral and dermal routes, minimally irritating to the eyes, not irritating to the skin, and did not cause an allergic skin reaction.

The end-use products Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies were of low acute toxicity via the oral and dermal routes of exposure in laboratory animals. They were not irritating to the eyes or skin and did not cause an allergic skin reaction. When administered to adult and young dogs, no adverse effects were observed at doses greatly exceeding those specified on the product labels.

There was no evidence to suggest that d-phenothrin damaged genetic material and it is not considered to be a potential human carcinogen. Although d-phenothrin exerts its action on the nervous system, there was little evidence of neurotoxicity. There was no indication that d-phenothrin caused damage to the immune system or affected the ability to reproduce. Health effects in animals given repeated doses of d-phenothrin included effects on the liver, adrenals and kidneys.

When given to pregnant or nursing rats, d-phenothrin caused slight, transient decreases in body weight of the young animal at doses which were not toxic to the mother, suggesting that the young were slightly more sensitive to d-phenothrin than the adult animal. Effects on the developing fetus (malformations) were noted following administration of d-phenothrin to pregnant rabbits. These effects occurred at doses which were also toxic to the mother.

The risk assessment protects against the effects of d-phenothrin by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Risks in Residential and Other Non-Occupational Environments

Residential risks are not of concern when Hartz UltraGuard Flea and Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies products are used according to label directions and instructions.

Exposure to d-phenothrin can occur when adults and youth handle these end-use products, and can come in direct contact with d-phenothrin residues on the skin. Adults, youth, and children can come in direct contact with d-phenothrin residues on the skin when contacting treated pets. In addition, children can ingest residues by hand-to-mouth activity after contacting treated dogs.

Residential exposures (application and postapplication) to the end-use products are not expected to result in unacceptable risk when these products are used according to label directions. Precautionary and hygiene statements on the label are considered adequate to protect individuals from unnecessary risk due to treatment or postapplication exposures.

Occupational Risks From Handling Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Flea and Tick Treatment for Dogs and Puppies products

Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Flea and Tick Treatment for Dogs and Puppies products are domestic products; therefore, no occupational assessments were conducted.

No occupational assessments were conducted.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

An environmental assessment is not required for applications to register spot-on products for use on companion animals as environmental exposure is negligible.

Value Considerations

What Is the Value of the Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies line of products and the Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies line of products?

Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies and Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies are spot-on products used to kill fleas and ticks and reduce biting by mosquitoes for up to 30 days on dogs and puppies over 12 weeks of age.

The Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies line of products kills fleas and ticks and reduces biting by mosquitoes for up to 30 days on dogs and puppies over 12 weeks of age. These products only target the flea adults. There are four (4) products available to treat the various sizes of dogs (i.e. 2.5-6 kg, 6-14 kg, 14-28 kg, over 28 kg).

The Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies line of products kills fleas and ticks and reduces biting by mosquitoes for up to 30 days on dogs and puppies over 12 weeks of age. In addition to killing adult fleas using d-phenothrin, these products contain the insect growth regulator, s-methoprene, to kill the eggs and larvae of fleas. Without s-methoprene, the product would only target the adults. There are four (4) products available to treat the various sizes of dogs (i.e. 2.5-6 kg, 6-14 kg, 14-28 kg, over 28 kg).

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the labels of the four Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies end-use products and the four Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies end-use products to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The hazard signal words "CAUTION-POISON" are required on the label

In the Precautions section, in addition to the statements "Causes moderate eye irritation" and "Avoid contact with eyes or clothing", the labels of the end-use products must include, "Wash hands, and any other skin that came into contact with the product, thoroughly with soap and water after handling or applying, and before eating, drinking, chewing gum or using tobacco".

As these products are a liquid formulation and a small volume is being used, there is no concern from exposure by the inhalation route.

Next Steps

Before making a final registration decision on d-phenothrin, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

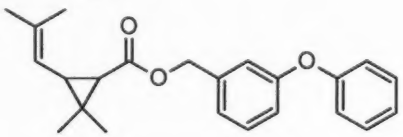
Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on d-phenothrin (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	d-phenothrin
Function	insecticide
Chemical name	
1. **International Union of Pure and Applied Chemistry (IUPAC)**	3-Phenoxybenzyl (1*RS*, 3*RS*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate
2. **Chemical Abstracts Service (CAS)**	(3-phenoxyphenyl)methyl (1*R*)-*cis-trans*-2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate
CAS number	26002-80-2 for the racemic mixture
Molecular formula	$C_{23}H_{26}O_3$
Molecular weight	350.46 g/mol
Structural formula	 (racemic structure shown)
Purity of the active ingredient	96.6%

1.2 Physical and Chemical Properties of the Active Ingredients and End-use Product

Technical Product—Sumithrin Technical Grade

Property	Result
Colour and physical state	yellow to yellowish brown
Odour	faint
Melting range	not applicable since the product is a liquid
Boiling point or range	> 290°C
Density	1.06 g/ml at 20°C
Vapour pressure at 20°C	0.0187 mPa
Ultraviolet (UV)-visible spectrum	λ_{max} at 273 and 279 nm
Solubility in water at 20°C	< 9.7 µg/L at (25°C)
Solubility in organic solvents at 25°C (g/100 mL)	Solvent — Solubility (mg/L) hexane — 4.96 methanol — 5.0
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = 6.01
Dissociation constant (pK_a)	not applicable since the product does not contain any dissociable moieties
Stability (temperature, metal)	hydrolysed by alkali

End-use Products— Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies

Property	Result
Colour	light amber to amber
Odour	solvent-like
Physical state	solution
Formulation type	solution
Guarantee	d-phenothrin at 85.70% (*S*)-methoprene at 2.30%
Container material and description	1.1-5.9 mL HDPE/PET plastic containers
Density	1.035 g/ml (at 25°C)
pH	7.1
Oxidizing or reducing action	The product has no oxidizing or reducing properties

Property	Result
Storage stability	The product was found to be stable for 12 months at ambient temperature (25°C)
Corrosion characteristics	No corrosion was detected upon storage for 12 months at ambient temperature (25°C)
Explodability	The product is not potentially explosive under normal use

End-use Products—Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies

Property	Result
Colour	light amber to amber
Odour	solvent-like
Physical state	solution
Formulation type	solution
Guarantee	d-phenothrin at 85.70% (*S*)-methoprene at 2.30%
Container material and description	1.1-5.9 mL HDPE/PET plastic containers
Density	1.035 g/ml (at 25°C)
pH of 1% dispersion in water	6.9
Oxidizing or reducing action	The product has no oxidizing or reducing properties
Storage stability	The product was found to be stable for 12 months at ambient temperature (25°C)
Corrosion characteristics	No corrosion was detected upon storage for 12 months at ambient temperature (25°C)
Explodability	The product is not potentially explosive under normal use

1.3 Directions for Use

The Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies line of products and the Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies line of products kill adult ticks and adult fleas and reduce biting by mosquitoes on dogs and puppies over 12 weeks of age for up to 30 days. In addition, the Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies line of products contain s-methoprene, which is responsible for killing flea eggs and nymphs. Both lines of products are applied in pre-packaged dosage tubes that are applied starting at the back of the neck and going to the tip of the tail and are to be re-applied at monthly intervals. The dosages are the same for both lines of products and are as follows: i) 0.56 ml product for dogs weighing 2.5-6 kg; ii) 1.3 ml for dogs weighing 6-14 kg; iii) 4.1 ml for dogs weighing 14-28 kg and; iv) 5.9 ml for dogs weighing over 28 kg. For further details, refer to the product labels.

1.4 Mode of Action

d-Phenothrin is a pyrethroid which stimulates the nerves to keep the sodium channels of insects open beyond their normal timing thresholds, causing paralysis and eventually death of the pest.

s-Methoprene is an insect growth regulator that acts by mimicking the action of the juvenile hormone keeping the insect in an immature state which results in its eventual death.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in d-phenothrin technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for the technical grade active ingredient, d-phenothrin, was conducted. The database was considered complete and consisted of the full array of toxicity studies currently required for hazard assessment purposes. The toxicology database supporting d-phenothrin was primarily based on studies available from the registrant and was considered adequate to define the majority of the toxic effects that may result from exposure.

d-Phenothrin is a type I synthetic pyrethroid insecticide. Pyrethroids delay the closing of neuronal voltage-dependant sodium channels, causing the depolarization of the neuron; this interferes with the ability of the nervous system to relay nerve transmissions and may result in downstream clinical effects. Technical d-phenothrin is predominantly a mixture of 1R, cis- and 1R, trans-isomers with a typical cis:trans isomer ratio of 20:80.

Radiolabelled d-phenothrin was rapidly absorbed and distributed following either single or repeated oral exposure in the rat. Tissue levels of radioactivity were low under all of the dosing regimens. Peak tissue levels were noted three hours post-dosing, with most of the radioactivity disappearing within twenty four hours following dosing. Residues of d-phenothrin were primarily located in the fat, with levels of radioactivity in fat associated with the trans-isomer being lower than those identified with the cis-isomer. For both isomers, levels of radioactivity were higher following repeated oral doses than following a single dose. There was little evidence of bioaccumulation potential with either of the dosing regimens.

With both isomers of d-phenothrin, major metabolites identified in both sexes of rat were 4'-hydroxyl-phenoxybenzoic acid-sulfate and 3-phenoxybenzoic acid. Urinary metabolites were derived following ester cleavage of the parent compound, whereas fecal metabolites of the cis-isomer retained the ester linkage and were derived from oxidation. The metabolite pattern appeared to be the same regardless of the dose regimen and no sex-related differences were apparent.

After administration of single doses of either isomer in rats, the primary route of excretion was the feces, with higher fecal excretion noted for the cis-isomer. After repeated dosing, the fecal route was still the predominant route for the cis-isomer whereas urinary excretion was the predominant route of elimination for the trans-isomer. Following either single or repeated dosing of d-phenothrin in rats, excretion was virtually complete within seven days of dosing. There was no detectable radioactivity in the expired air of rats treated with single or repeated oral doses of the cis- or trans-isomer of d-phenothrin.

In rats, technical d-phenothrin was of low acute toxicity by the oral and dermal routes and slightly toxic by the inhalation route of exposure. d-Phenothrin was minimally irritating to the eyes of rabbits but was not a skin irritant in rabbits or a potential skin sensitizer in the Maximization test when tested with guinea pigs. Clinical signs of toxicity were noted only in the acute inhalation toxicity studies and included slight excitation, laboured breathing, rales, nasal discharge, dried red material on the facial area, chromodacryorrhea and urinary incontinence.

The end-use products Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies were of low acute toxicity via the oral and dermal routes of exposure in rats and rabbits, respectively. They were not irritating to the eyes or skin of rabbits and did not cause an allergic skin reaction when tested in guinea pigs in the Buehler test. When administered to adult and young dogs, no adverse effects were observed at doses greatly exceeding those specified on the product labels.

Repeated oral and inhalation administration of d-phenothrin to mice, rats and dogs revealed that the target organ was the liver with increased organ weights noted at lower dosage levels followed by increased enzyme levels and histopathology (hepatocellular hypertrophy, coagulative liver necrosis and bile duct proliferation) at higher dosage levels. Toxicologically significant effects on the adrenal gland (organ weight increases and histopathological alterations) and the kidney (increased organ weights and alterations in clinical chemistry) were also noted at higher dosage levels. Additional effects seen in the 90-day inhalation study in rats included eosinophilic inclusions in the olfactory epithelial cells of the nasal turbinates and clinical signs of toxicity (poorly groomed fur, dirty tails and a reduced response to a knock on the chamber door). In a 21-day dermal toxicity study, no signs of systemic toxicity were noted in rats receiving the limit dose of 1,000 mg/kg bw/day. Based on the results of these repeat-dose toxicity studies, the dog appeared to be the most sensitive species. As well, it was noted that prolonging the duration of exposure (i.e. from intermediate to chronic durations) to d-phenothrin by the oral route led to increased toxicity in rats and dogs.

In a two-year dietary chronic toxicity/carcinogenicity study in mice, exposure to d-phenothrin did not result in any overt signs of toxicity or effects on survival. An increased incidence of hepatocellular adenomas was noted in both sexes while an increased incidence of hepatocellular carcinomas was noted only in females exposed to d-phenothrin. The increased incidence of hepatocellular adenomas noted in males was slightly above the historical control range provided by the registrant but did not demonstrate any progression to hepatocellular carcinomas. In females, the incidence of hepatocellular adenomas was within the historical control range; however, the incidence of hepatocellular carcinomas was only slightly above the historical control range at the high-dose level. Given that the increase in the combined incidence of adenomas and carcinomas in female rats was not statistically significant and only marginally exceeded the historical control range, the level of concern was considered low for these tumours.

In rats, a two-year dietary chronic toxicity/carcinogenicity study demonstrated a marginally increased incidence of adenomas and carcinomas of the preputial gland at a dosage level of 141 mg/kg bw/day. In a second rat carcinogenicity study, there was no evidence of preputial tumours, even at significantly greater dosage levels. In view of these findings, the overall weight of evidence suggested a low level of concern for preputial gland tumours in rats. In the second two-year study, an increased incidence of hepatocellular adenomas and carcinomas was noted in high-dose males and females along with an increased incidence of uterine adenomas and adenocarcinomas in high-dose females. The increased incidence of tumours at the high-dose level was of limited concern given the fact that this dosage level resulted in severe liver toxicity and clearly exceeded the maximum tolerated dose.

d-Phenothrin showed no evidence of mutagenicity, with or without metabolic activation, in in vitro bacterial/microsomal reverse mutation studies with *Salmonella typhimurium* or *Escherichia coli*. Negative results were also noted in an in vitro unscheduled DNA synthesis assay in HeLa S3 human cells. No evidence of clastogenic potential was noted in an in vitro chromosomal aberration assay conducted with Chinese hamster ovary cells, or in an in vivo assay conducted with the bone marrow cells of ICR mice.

Two multi-generation dietary reproduction toxicity studies were conducted with rats. In the first of these studies, effects on the development of the offspring were noted only at dosage levels resulting in maternal toxicity. Therefore, sensitivity of the young was not demonstrated in this study. In the more recent two-generation rat reproductive toxicity study, decreased pup weight was noted in the second generation offspring from postnatal days 1 to 14, in the absence of maternal toxicity. At higher dosage levels, more significant effects in the pups (i.e. effects on survival) were noted in the presence of severe maternal toxicity. Results of this study suggested sensitivity of the young; however, given that the effect on pup body weight occurred only in the second generation, was transient, and of a small magnitude, the concern for sensitivity was low.

In a developmental toxicity study in rats, oral gavage administration of d-phenothrin resulted in reduced maternal and fetal body weights, delayed ossification and fetal immaturity (dilation of the brain ventricles and space between the body wall and organs) at the same dosage levels. Since developmental effects were only observed at maternally toxic dose levels, it was concluded that increased susceptibility of the young was not demonstrated through in utero exposure.

In an oral gavage rabbit developmental toxicity study, maternal toxicity in the form of weight loss, decreased body weight gain and food consumption was noted starting at 300 mg/kg bw/day. An increased number of abortions were observed at the highest dose tested of 500 mg/kg bw/day. At 500 mg/kg bw/day, four fetuses from three separate litters displayed hydrocephaly; the incidence exceeded historical control data and was considered treatment-related. Sensitivity of the young was not demonstrated in rabbits as the effects in the developing fetus were observed only in the presence of maternal toxicity.

In an acute neurotoxicity study conducted via the oral route with rats, no clinical signs of toxicity, effects on motor activity, or adverse histopathology were noted. Similarly, in a 13-week oral neurotoxicity study, no evidence of neurotoxicity was noted in rats. The effects that were noted in this repeat-dose study were limited to decreased body weight, body weight gain and food consumption; however, it should be noted that only a limited number of parameters are examined in studies of this type. The d-phenothrin toxicity database as a whole showed little to no evidence of neurological signs typically associated with pyrethroids.

Uterotrophic and Hershberger assays with d-phenothrin were reported in the published literature. Based on the results of these two in vivo assays, it was concluded that d-phenothrin did not exhibit any potential to cause adverse estrogenic or (anti-) androgenic effects at dosage levels up to and including 1000 mg/kg bw/day.

Despite a lack of strong evidence of increased sensitivity of the offspring in any of the submitted studies, residual uncertainty remains regarding susceptibility of the young. Literature studies indicate that pharmacodynamic and pharmacokinetic factors, notably age-dependent maturation of key metabolic processes, may lead to increased susceptibility of the young to pyrethroid toxicity. Young animals have incomplete maturation of the enzyme systems that detoxify pyrethroids, particularly the carboxylesterases and cytochrome P450s. Consequently, pyrethroid concentrations in target tissues (for example, brain) may be higher in young animals than in adults given the same dose. In general, pyrethroid neurotoxicity is correlated to peak concentrations of the compound, with gavage dosing patterns resulting in greater internal doses compared to dietary administration. The pyrethroids are regarded as having a narrow window of time-to-peak-effect. The design of a developmental neurotoxicity study does not consider time-to-peak-effect and may miss the window of peak toxicity for the pyrethroids. Accordingly a developmental neurotoxicity study is not required for d-phenothrin.

Behavioral assessments were conducted at the time-to-peak effect in adults in an acute neurotoxicity study with d-phenothrin; however, behavioral assessments were not conducted in offspring. In the recent evaluation of other pyrethroids, a similar situation has resulted in the application of a database uncertainty factor for the lack of a comparative oral gavage neurotoxicity study considering time-to-peak effect in pups, weanlings and adult animals. This factor has not been applied in the case of d-phenothrin in view of the lack of neurotoxicity noted in the animal toxicity data. Endpoints selected for risk assessment were well below the dose levels employed and without effect in adult animals in the acute neurotoxicity study, thus affording intrinsic protection to the young for potential neurotoxicity.

Results of the toxicology studies conducted on laboratory animals with d-phenothrin, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Appendix I, Tables 1 and 2.

3.1.1 Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA. Information on the reporting of incidents can be found on the PMRA website. Incidents were searched and reviewed for d-phenothrin. As of July 4, 2012, a total of 17 human and 161 domestic animal incidents involving d-phenothrin have been reported to the PMRA. Of these, the symptoms reported in 10 human and 138 domestic animal incidents were considered to have at least some degree of association with exposure to the pesticide. The most commonly reported symptoms in human incidents were minor in severity and included skin and eye irritation, coughing, and headache.

The majority of the domestic animal incidents (70%) were deaths that occurred in the United States, which represent only a sub-set of all of the incidents that occur in the United States since registrants are only required to report to the PMRA domestic animal deaths and not United States incidents of lesser severity. When deaths in the United States are excluded, the majority of the domestic animal incidents (78%) were minor to moderate in severity. Lethargy, anorexia, vomiting, seizure, muscle tremors, diarrhea, and ataxia were reported most frequently in domestic animal incidents.

Spot-on liquid products for the control of fleas and ticks on dogs were implicated in a high number of incidents, several of which involved species misuse (i.e. the product was used on a cat). In Canada, spot-on liquid products containing d-phenothrin which are also registered in the United States were involved in 6 incidents involving dogs, two of which were minor in severity, while the other four were considered moderate. Most incidents (>90%) that occur in the United States involving d-phenothrin spot-on products used on dogs are minor to moderate in severity. As part of its ongoing evaluation of incident reports related to spot-on flea and tick products, the PMRA will monitor for future incidents related to d-phenothrin spot-on liquids.

Given the absence of frank neurological signs in the toxicity database, the incident report findings were somewhat unexpected; however, the influence of factors such as formulants (some of which are no longer used), misuse, and health status cannot be discounted. The labels for the associated end-use products will be required to comply with the standards as specified in Regulatory Directives DIR2002-01, *Canadian Label Improvement Program for Pesticides Used on Companion Animals* and DIR2010-02, *Label Improvements for Spot-on Pesticides Used for Flea and Tick Control on Companion Animals*.

3.1.2 Pest Control Products Act Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the exposure of and toxicity to infants and children, extensive data were available for d-phenothrin. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and two multi-generation reproductive toxicity studies in rats. A comparative neurotoxicity study was not available but given the lack of neurotoxic findings throughout the d-phenothrin database, the results of such a study, in this case, would not be expected to significantly affect the risk assessment.

With respect to potential prenatal and postnatal toxicity, decreased pup weight was noted in the second generation of the two generation rat reproduction toxicity study in the absence of maternal toxicity. At higher dosage levels, more significant effects in the pups (i.e. effects on survival) were noted in the presence of severe maternal toxicity. Results of this study demonstrated sensitivity of the young; however, there was a low level of concern given the fact that the magnitude of the effect on the body weight of the pups was slight and recovery was noted prior to weaning of the pups.

In a developmental toxicity study in rats, there was an increased incidence of delayed ossification and fetal immaturity as demonstrated by dilation of the brain ventricles and space between the body wall and organs, in the presence of maternal toxicity. In a rabbit developmental study, an increased incidence of abortions and malformations (hydrocephaly) was noted at a maternally toxic dosage level.

Overall, the database is adequate for determining the sensitivity of the young and effects on the young are well characterized. Although the fetal effects in the rabbit developmental toxicity study were considered serious endpoints, the concern was tempered by the presence of maternal toxicity suggesting that a 3-fold *Pest Control Products Act* factor would be required. Since the selected endpoints for risk assessment provide an intrinsic margin to the malformations, the *Pest Control Products Act* factor has been reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

Establishment of an acute reference dose is not required as there are no proposed food uses.

3.3 Acceptable Daily Intake (ADI)

Establishment of an acceptable daily intake is not required as there are no proposed food uses.

3.4 Cancer Assessment

Since there was no clear evidence of carcinogenicity at doses below the maximum tolerated dose, a cancer risk assessment was not conducted.

3.5 Occupational and Residential Risk Assessment

Residential handler and postapplication exposures to Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Flea and Tick Treatment for Dogs and Puppies products is characterized as short- to intermediate-term, and is predominantly by the dermal route.

3.5.1 Toxicological Endpoints

Short- and Intermediate-term Dermal

For occupational and residential short- and intermediate-term dermal risk assessment, the 21-day dermal toxicity study conducted with rats was selected. In this study, there were no treatment-related effects noted at the NOAEL (no observed adverse effects level) and highest dose tested of 1000 mg/kg bw/day. The target margin of exposure (MOE) for this scenario was 100, which accounted for a 10-fold uncertainty factor for interspecies extrapolation and a 10-fold uncertainty factor for intraspecies variability. When converted into an oral equivalent dose using a dermal absorption value of 16%, the dermal dose of 1000 mg/kg bw/day provides a margin slightly less than the desired 300 to the developmental toxicity endpoint in rabbits. However, since this dermal absorption value is considered to be an over-estimate of absorption, no additional uncertainty factors were deemed necessary. For residential exposures, the *Pest Control Products Act* factor was reduced to 1-fold. This MOE was considered to be protective of all populations including pregnant women and their fetuses, infants and children.

Non-Dietary Oral Ingestion (Children, Short-term)

For non-dietary oral ingestion risk assessment, the developmental toxicity study in the rabbit was selected. In this study, a NOAEL of 100 mg/kg bw/day was selected based on weight loss, decreased body weight gain and food consumption that occurred at the next dosage level. These effects are endpoints that could result from a short-term exposure and therefore are considered relevant for this scenario. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The target MOE for this scenario was 100.

Aggregate Assessment

No endpoints were selected for short- or intermediate-term aggregate assessment. Endpoints from route-specific studies were dissimilar (generalized toxicity in oral studies versus local effects in the inhalation studies) or non-existent (absence of effects at limit dose in dermal study).

3.5.1.1 Dermal Absorption

A dermal absorption value of 16% has been used for the registration of other products containing d-phenothrin. However, no dermal absorption value is required for the present assessments since the toxicological endpoint selected for short- to intermediate-term dermal exposure is a NOAEL from a dermal toxicity study.

3.5.2 Occupational Exposure and Risk

Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Flea and Tick Treatment for Dogs and Puppies products are domestic products; therefore, occupational exposure assessments were not conducted.

3.5.3 Residential Exposure and Risk Assessment

A quantitative risk assessment was only conducted for d-phenothrin for the current use pattern, as the exposure to s-methoprene from the Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies products is within the exposure of currently registered pet products containing s-methoprene. The assessment of d-phenothrin applies to both sets of Hartz products as they contain the same amount of the active ingredient which can be handled or dislodged from treated dogs.

3.5.3.1 Handler Exposure and Risk

Individuals (adults and youth) have potential for exposure to Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies and Hartz UltraGuard Flea and Tick Treatment for Dogs and Puppies products during application. Dermal and inhalation exposure estimates for residential users were generated using the revised (2001) EPA Standard Operating Procedures for Residential Exposure Assessments, as chemical-specific data for assessing human exposures during pesticide handling activities were not submitted.

Exposure to residents applying Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Flea and Tick Treatment for Dogs and Puppies products is expected to be short- to intermediate-term in duration and to occur primarily by the dermal route. Exposure estimates were derived for pet owners applying the products to dogs and puppies using ready-to-use squeeze tubes containing pre-measured volumes of the product. A pet owner was assumed to apply no more than one tube to the lowest weight dog among the ranges of weights for each product. The exposure estimates are based on the pet owners wearing no personal protection equipment.

Dermal exposure was estimated by coupling the amount of product handled per dog, the fraction of the product available for transfer to the pet owner, and treating one dog per day. Inhalation exposure was considered negligible. Exposure was normalized to mg/kg bw/day by using 70 kg adult and 39.1 kg youth body weights.

Exposure estimates were compared to the dermal NOAEL to obtain the MOE; the target MOE is 100.

Table 1 Homeowner Application Dermal Exposure and Risk Estimates

Residential Scenario	Maximum Application rate (mg a.i./dog)	Fraction of a.i. available for exposure	Exposure[a] (mg/kg bw/day)	Margin of Exposure[b] (target = 100)
Adults (18+)	5233	0.01	0.748	1340
Youth (10-12)	5233	0.01	1.34	746

Only one dog treated in a day

[a] Dermal Exposure Estimate = Application Rate * Fraction available for transfer to skin / Body Weight
Where, Body Weight = 70 kg adult, 39.1 kg youth

[b] $MOE_{Dermal} = \frac{NOAEL_{Dermal}\ (mg/kg\ bw/day)}{Exposure\ estimate\ (mg/kg\ bw/day)}$
Where, NOAEL = 1000; target MOE = 100

Dermal MOEs were greater than the target MOE of 100. Therefore, the risks to pet owners (adults and youth) applying the product to dogs and puppies are not expected to be of concern.

3.5.3.2 Postapplication Exposure and Risk

There is potential for exposure to adults, youth, and children when contacting dogs treated with Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Flea and Tick Treatment for Dogs and Puppies products. Potential postapplication exposure can result from interacting with treated pets while petting, playing, and grooming. The primary route of postapplication exposure for contacting treated pets would be through the dermal route for adults, youth, and children. A quantitative dermal risk assessment was based on the highest volume of product that can be applied to a dog (5.9 ml). Inhalation is not considered to be of concern for pet products. Oral hand-to-mouth, non-dietary exposure for children (three years old) may also occur. The duration of exposure is considered to be short- to intermediate-term. No dissipation of the product is taken into account, as residents can contact a treated dog as soon as the treatment has been applied.

3.5.3.2.1 Postapplication Dermal Exposure and Risk Estimates

Dermal exposures of adults, youth, and children contacting treated dogs are estimated by using the assumptions and defaults from the USEPA Residential SOP (2001). In the absence of chemical-specific residue data, it is assumed that individuals contact treated pets on the same day the product is applied. There is no scenario for the assessment of spot-on treatments; however, it is assumed that the flea collar scenario is the most appropriate scenario to use as a surrogate. The amount of dislodgeable residue is 20% of the amount applied, assuming the total amount of the active ingredient is evenly distributed over the whole dog, and the fraction of the dislodgeable residue that is transferred to an individual is 10%.

Exposure estimates were compared to the toxicological endpoint to obtain the MOE; the target MOE is 100.

Table 2 Postapplication Dermal Exposure and Risk Estimates

Scenario	Maximum Application Rate (mg)	Exposure [a] (mg/kg bw/day)	Margin of Exposure [b] (Short- to intermediate- term; target MOE = 100)
Adult	5233	1.495	668
Youth		2.677	373
Child		6.977	143

[a] Dislodgeable residue assumed to be 20% of the application rate x Fraction of dislodgeable residue transferred to an individual assumed to be 10% / Body Weight
Where, body weight (kg) = adult,70; youth, 39.1; and child, 15

[b] $MOE_{Dermal} = \frac{NOAEL_{Dermal}\ (mg/kg\ bw/day)}{Exposure\ estimate\ (mg/kg\ bw/day)}$
Where, NOAEL =1000; target MOE = 100

Dermal MOEs were greater than the target MOE of 100. Therefore, the risks to adults, youth, and children dermally contacting treated dogs and puppies are not expected to be of concern.

3.5.3.2.2 Toddler hand-to-mouth exposure

Toddler hand-to-mouth transfer from contacting treated dogs is estimated based on the USEPA Residential SOP updates (2001). The 2001 updates, primarily for lawn care pesticides, indoor broadcast treatments, and crack and crevice treatments, include assumptions that are not affected by the contact scenario. The value for the surface area that is mouthed is 20 cm^2, for one to three fingers. Also, the 2001 Residential SOP recommends using a value of 50% for saliva extraction from the hands. The intermediate-term frequency of hand-to-mouth contacts is used, as this activity will take place over the entire treatment regime of several months. Therefore, the 1997 version of the algorithm has been amended to reflect the 2001 updated assumptions.

$DR = AR * F / SA_{Pet}$

Where, DR = Dislodgeable Residue (mg/cm^2 pet);
AR = Application Rate (mg of d-phenothrin for each product);
F = Fraction of a.i. available for transfer (0.20 unitless);
SA_{Pet} = Surface area of dog (cm^2) = 12.3 * (dog body weight (kg) * 1000)$^{0.65}$

$E = DR * SA * FQ * SEF * ET / BW$

Where, E = Exposure (mg/kg bw/day);
DR = Dislodgeable Residue (mg/cm^2 pet);
SA = Surface area of one to three fingers (20 cm^2);
FQ = Frequency of hand-to-mouth activity (9.5 times/hour);
SEF = Saliva Extraction Factor (50% = 0.5);
ET = Exposure time (2 hrs/day);
BW = Toddler body weight (= 15 kg)

Table 3 Toddler Hand-to-Mouth Oral Exposure and Risk Estimates

Dog weight (kg) ranges	Amount of d-phenothrin per treatment[a] (1 tube) (mg a.i./tube/dog)	Dog body surface area[b] (cm^2)	Dog (lower weight) dislodgeable residue (mg/cm^2)	Exposure (mg/kg bw/day)	Margin of Exposure[c] Short- to intermediate-term (target = 100)
2.3–5.8	577	1884	0.0613	0.776	128
5.9–14	1153	3475	0.0664	0.841	118
14.1–28	3637	6122	0.119	1.51	66
>28	5233	9584	0.109	1.38	72

a. Based on the amount of active ingredient available in the treatment tube while treating the lowest weight dog in the range
b.; USEPA Residential SOP (2001), calculation amended from US EPA (1993) Wildlife Exposure Factors Handbook
c. d-phenothrin NOAEL 100 mg/ kg bw/day for short- and intermediate-term incidental oral exposures

Although the hand-to-mouth risks for the two largest tube sizes in each of the product sets, 4.1 mL (MOE = 66) and 5.9 mL (MOE = 72), do not meet the target MOE of 100, the daily exposure duration is likely less than two hours for contact and hand-to-mouth activity for a toddler (three years old). The 2-hour duration is based on children's playing time outdoors. However, the 1997 EPA Exposure Factors Handbook lists the time spent on animal care for 1-4 years old as 59.2 minutes (mean) with standard deviation of 44.3 (n=9). The same table is used in the 2011 Exposure Factors Handbook. Therefore, exposure is overestimated by a factor of two. Taking this into consideration, the risks for child hand-to-mouth activities, when contacting dogs treated with the 4.1 mL and 5.9 mL tube sizes, are considered acceptable.

3.5.3.3 Bystander Exposure and Risk

Bystander exposure is considered to be negligible compared to the residential adult, youth, and child exposures.

3.5.3.4 Aggregate Exposure and Risk Assessment

Adults and youth can treat dogs and contact the treated dogs immediately after the treatments. Therefore, application and postapplication exposures for these individuals should be aggregated. Dermal and oral exposures for toddlers are not aggregated since oral and dermal NOAELs are not based on the same toxicological effect.

Table 4 Dermal Aggregate Risk for Applicator and Postapplication

Sub-population	Applicator MOE[a]	Postapplication MOE[b]	Total MOE method [c] Short- to intermediate-term aggregate; (target MOE = 100)
Adults	1340	668	445
Youth	746	373	249

a. From Table 2
b. From Table 3
c. Aggregate determined according to SPN2003-04; NOAEL of 1000 mg/kg bw/day

All aggregated risks for short- to intermediate-term durations are greater than the target Margin of Exposure of 100. Scenarios of adults and youth who treat dogs and contact treated dogs are considered acceptable.

4.0 Impact on the Environment

An environmental assessment is not required for applications to register spot-on products for use on companion animals as environmental exposure is negligible.

5.0 Value

5.1 Effectiveness Against Pests

Eight trials investigating the efficacy of formulations equivalent to the Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies and Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies were used to support the label claims. The trials consisted of six studies against fleas (adults and usually eggs), six studies against ticks (adults) and one study against mosquitoes on dogs weighing between 4.7 to 37.4 kg with the amount of product applied ranging from 1.1 to 4.6 ml. The average dosage for these studies ranged between 0.14 to 0.19 ml product/kg of dog. An additional laboratory study comparing the efficacy of Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies against two species of tick, brown dog tick and American dog tick, was used as supplemental information.

The efficacy data supported the claim that the Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies kill fleas (adults) and ticks (adults) and reduce biting by mosquitoes for up to 30 days.

The efficacy data supported the claim that the Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies kill fleas (eggs, larvae, adults) and ticks (adults) and reduce biting by mosquitoes for up to 30 days.

5.1.1 Acceptable Efficacy Claims

The Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies series of products kill fleas (adults) and ticks (adults) and reduce biting by mosquitoes on dogs and puppies over 12 weeks old for up to 30 days.

The Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies series of products kill fleas (eggs, larvae, adults) and ticks (adults) and reduce biting by mosquitoes on dogs and puppies over 12 weeks old for up to 30 days.

5.2 Sustainability

5.2.1 Survey of Alternatives

Alternative chemistries registered in Canada for use on dogs against fleas, ticks and mosquitoes are located in Appendix I, Table 5. Most of the alternatives belong to the following mode of action (MOA) groups: carbamates (MOA 1A), organophosphates (MOA 1B) and pyrethroids (MOA 3A). There are also active ingredients containing neonicotinoids (MOA 4A), juvenile hormone mimics (MOA 7A&C), amitraz (MOA 19), rotenone (MOA 21) and potassium salts of fatty acids. Of these, the carbamates are being proposed for phase-out and the registration of rotenone for these uses expires 31 December 2012.

5.2.2 Compatibility with Current Management Practices Including Integrated Pest Management

The use of these products is compatible with current management practices. As per DIR2002-01, *Canadian Label Improvement Program for Pesticides Used on Companion Animals*, statements appear on the labels of these products recommending sanitation practices and use of these products with insecticidal premise treatments if pest problems continue.

5.2.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

The products do not contain a novel mode of action. There are several other products containing pyrethroids registered for use on dogs against fleas, ticks and/or mosquitoes. S-methoprene is also registered against fleas on dogs. To combat resistance, these products can be used in rotation with other registered products having active ingredients with a different mode of action. For a list of potential alternatives, please refer to Appendix I, Table 5.

Non-chemical techniques such as good sanitation practices (for example, vacuuming, laundering animal bedding) and reducing suitable habitat (for example, elimination of standing water required for mosquito reproduction, elimination of unmanaged vegetation) reduce pest populations in the environment.

As per DIR2002-01, *Canadian Label Improvement Program for Pesticides Used on Companion Animals*, a statement that a veterinarian should be consulted if the pests continue to be a problem is located on the product labels. A veterinarian would be able to provide additional guidance on alternative techniques to combat potential resistance issues.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, d-phenothrin and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

d-Phenothrin does not meet Track 1 criteria, and is not considered a Track 1 substance. See Appendix 1, Table 4 for comparison with Track 1 criteria.

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[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade d-phenothrin and the eight end-use products (Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies Weighing either 2.5-6 kg, 6-14 kg, 14-28 kg or over 28 kg; and Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies Weighing either 2.5-6 kg, 6-14 kg, 14-28 kg or over 28 kg) do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

- The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for d-phenothrin is adequate to define the majority of toxic effects that may result from exposure. In short-term and chronic studies on laboratory animals, the primary target was the liver, with the kidneys and adrenal gland affected at higher doses. There was no evidence to suggest that d-phenothrin damaged genetic material and it is not considered to be a potential human carcinogen. Although d-phenothrin exerts its action on the nervous system, there was little evidence of neurotoxicity. There was no indication that d-phenothrin caused damage to the immune system or affected the ability to reproduce. In a reproductive toxicity study, a slight, transient decrease in body weight was noted in pups from the second generation at doses which were not toxic to the mother. In a developmental toxicity study in rabbits, effects on the developing fetus (malformations) were noted, but only in the presence of maternal toxicity. The risk assessment protects against the toxic effects noted above

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6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Quantitative risk assessments for d-phenothrin were conducted for ready-to-use, spot-on pet care products for dogs. Residential exposures to individuals handling and contacting treated dogs, including toddlers, are not expected to result in unacceptable risk when Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies, and Hartz UltraGuard Flea and Tick Treatment for Dogs and Puppies products are used according to label directions.

7.2 Environmental Risk

An environmental assessment is not required for applications to register spot-on products for use on companion animal as environmental exposure is negligible.

7.3 Value

The value information supports the use of both the Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies line of products and Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies line of products against adults of fleas, ticks and mosquitoes on dogs and puppies for up to 30 days. The addition of s-methoprene in the Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies line of products also supports the claims against all life stages of fleas for up to 30 days.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Sumithrin Technical Grade (containing the active ingredient d-phenothrin) and eight domestic end-use products; four products containing d-phenothrin (Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies Weighing either 2.5-6 kg, 6-14 kg, 14-28 kg or over 28 kg), and four products containing a combination of the active ingredients s-methoprene and d-phenothrin (Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies Weighing either 2.5-6 kg, 6-14 kg, 14-28 kg or over 28 kg). All eight end-use products are spot-on products used to kill fleas and ticks and reduce biting by mosquitoes.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

%	percent
°C	degree(s) Celsius
µg	microgram(s)
a.i.	active ingredient
ADI	acceptable daily intake
A/G	albumin/globulin ratio
ALB	albumin
ALP	alkaline phosphatase
ALT	Alanine aminotransferase
AR	application rate
ARfD	acute reference dose
AST	Aspartate aminotransferase
BAF	bioaccumulation factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
BW	toddler body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CBI	confidential business information
CEPA	*Canadian Environmental Protection Act*
cm^2	centimetre(s) squared
DNA	deoxyribonucleic acid
DR	dislodgeable residue
E	exposure
ET	exposure time
F	fraction of a.i. available for transfer
F_1	first generation
F_2	second generation
fc	food consumption
FQ	frequency of hand to mouth activity
g	gram(s)
GD	gestation day
HDPE	high density polyethylene
HDT	highest dose tested
Hct	hematocrit
Hgb	hemoglobin
hr(s)	hour(s)
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LAP	Leucine aminopeptidase
LC_{50}	lethal concentration 50%

LD	lactation day
LD_{50}	lethal dose 50%
LDH	lactate dehydrogenase
LOAEL	lowest observed adverse effect level
MAS	maximum average score
mg	milligram(s)
MIS	maximum irritation score
ml	millilitre(s)
MOE	margin of exposure
mol	mole
mPa	milliPascal(s)
MTD	Maximum tolerated dose
NADPH	Nicotinamide adenine dinucleotide phosphate
nm	nanometre(s)
NOAEL	no observed adverse effect level
PCPA	*Pest Control Product Act*
PET	polyethylene terephthalate
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
RBC	red blood cells
SA	surface area
SEF	saliva extraction factor
SOP	standard operating procedures
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
U.S.	United States of America
USEPA	United States Environmental Protection Agency
UV	ultraviolet
wk(s)	week(s)
wt(s)	weight(s)

Appendix I Tables and Figures

Table 1 **Toxicity Profile of Hartz End-use Products Containing d-phenothrin** (Hartz UltraGuard Flea & Tick Treatment for Dogs and Puppies; Hartz UltraGuard Pro Flea and Tick Treatment for Dogs and Puppies)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague Dawley rats PMRA #1874104	LD_{50} > 5000 mg/kg bw Low toxicity
Acute dermal toxicity New Zealand White rabbits PMRA #1874103	LD_{50} > 2000 mg/kg bw Low toxicity
Eye irritation New Zealand White rabbits PMRA #1874101	MAS = 1.4, MIS = 8 at 1 hr Minimally irritating
Dermal irritation New Zealand White rabbits PMRA #1874100	MAS = 0.13, MIS = 0.9 at 1 hr Minimally irritating
Dermal sensitization (Buehler test) Hartley guinea pigs PMRA #1874099	 Non-sensitizer
Companion animal safety study Adult Beagle dogs PMRA #1874090	No compound-related effects were observed when animals received topical doses at 5times the label rate.
Companion animal safety study Beagle puppies PMRA #1874092	No compound-related effects were observed when animals received topical doses at 5times the label rate.

Table 2 Toxicity Profile of d-phenothrin

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Pharmacokinetic study Sprague-Dawley rats PMRA # 1216239, 2221847	Absorption: d-phenothrin was rapidly absorbed after both single (4 or 200 mg/kg bw) and repeated (4 mg/kg bw/day) oral doses. Distribution: Tissue residues were low with radioactivity identified primarily in the fat for both isomers. Fat levels of the trans-isomer were 2 to 10% lower than those of the cis-isomer. Tissue levels were higher following repeated doses than following a single dose with the concentration of radioactivity in the brain, liver, kidney and blood reaching maximum levels 3 hrs post-dosing. At 24 hrs post-dosing, the concentration of radioactivity in these tissues decreased to one-tenth to one-twentieth of the maximum concentration that was noted 3 hrs post-dosing. Compared to the liver and kidneys, the brain contained a small amount of radioactivity. Metabolism: Most urinary metabolites were derived following ester cleavage. The major metabolites identified in the urine and feces were 3-(4'-hydroxy) phenoxybenzoic acid and 3-phenoxybenzoic acid. A major metabolite identified in the feces was intact d-phenothrin which was considered to be unabsorbed material. The metabolite pattern appeared to be the same regardless of the dose regimen. Excretion: Following either single or repeated doses of both cis- and trans-isomers, excretion of administered radioactivity was virtually complete within 7 days (96 to 100% recovered). After single doses of either isomer, the primary route of excretion was the feces (range of 55.9 to 86.6%) with fecal excretion higher for the cis-isomer. Urinary excretion after single doses of either isomer ranged from 10.8% to 40.1%. After repeated doses, the fecal route was still the predominant route for the cis-isomer (feces: 71.7 to 72.9%) while the urinary excretion was the predominant route of elimination for the trans-isomer (urine: 70.3 to 74.9%). There was no detectable radioactivity in expired carbon dioxide. Whole-body autoradiography: The radioactivity was rapidly distributed into tissues and organs following dosing. The greatest concentration of radioactivity in the tissues was found 3 hrs post-dosing. At 24 hrs post-dosing, most of the radioactivity disappeared from the tissues. No significant sex differences were identified in distribution, metabolism or excretion.

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA # 2222322	LD_{50} > 5,000 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA # 1157417	LD_{50} > 2,000 mg/kg bw Low toxicity
Acute inhalation toxicity ICR mice PMRA # 2126786	LC_{50} > 1.18 mg/L Slight toxicity
Acute inhalation toxicity Sprague-Dawley rats PMRA # 2126819, 2126786	LC_{50} >1.18 to 2.1 mg/L Low to slight toxicity
Eye irritation New Zealand White rabbits PMRA # 1142183	MAS = 0.33 MIS = 1, at 1 and 24 hr Minimally irritating
Dermal irritation New Zealand White rabbits PMRA # 1142183	MAS = 0 MIS = 0 Non-irritating
Dermal sensitization (Maximization test) Hartley guinea pigs PMRA # 1142184	 Non-sensitizer
5-Week range-finding dietary toxicity study B6C3F1 mice PMRA # 1233959	No NOAEL established (range-finding) Effects observed at ≥230 mg/kg bw/day included the liver and the kidneys.
13-Week dietary toxicity study F344 rats PMRA # 1142584, 1233961	NOAEL = 70/75 mg/kg bw/day LOAEL = 216/227 mg/kg bw/day Based on ↓ total cholesterol; ↑ ALP (5 wks) and A/G ratio, ↓ absolute spleen wt (♂); ↑ total plasma protein and ALB, ↑ liver wts (♀)

Study Type/Animal/PMRA #	Study Results
6-Month dietary toxicity study Sprague-Dawley rats PMRA # 1143141	NOAEL = 150 mg/kg bw/day LOAEL = 500 mg/kg bw/day Based on ↓ bwg, ↑ ALB, A/G ratio and BUN, ↓ sodium, ↑ kidney, liver and adrenal wts; ↑ absolute liver wts, ↓ RBC, Hgb and Hct, ↑ BUN and serum cholesterol, dilatation of the retinal vessels (♂); ↓ bw, ↓ water intake and serum cholinesterase activity, ↑ relative thyroid and kidney wts, ↑ ALP, ↑ lymphocytes and ↓ neutrophils, ovarian cysts filled w/fluid (♀)
5-Day range-finding oral toxicity study New Zealand White rabbits PMRA # 1227040	No NOAEL established (range-finding) Effects noted at 250 mg/kg bw/day or above included clinical signs.
26-Week dietary toxicity study Beagle dogs PMRA # 2126801, 2126802, 2126804, 2126806	NOAEL = 32/33 mg/kg bw/day (HDT) LOAEL not established
52-Week dietary toxicity study Beagle dogs PMRA # 1216240	NOAEL = 8.2/7.1 mg/kg bw/day LOAEL = 28/27 mg/kg bw/day Based on ↓ ALB and A/G ratio, pituitary microcysts; focal degeneration of adrenal cortex with mononuclear cell infiltration of adrenal glands, diffuse hepatocellular enlargement, focal mononuclear infiltration of epididymides
21-Day dermal toxicity study CD rats PMRA # 1157418	NOAEL = 1,000 mg/kg bw/day No systemic effects observed. Desquamation of the skin observed in ♀ at ≥100 mg/kg bw/day and in ♂ at 1,000 mg/kg bw/day
4-Week inhalation toxicity study ICR mice PMRA # 2126786	NOAEL = 0.06 mg/L LOAEL = 0.21 mg/L Based on ↑ liver wts; ↑ Hgb, Hct and sedimentation values, ↑ pituitary and absolute adrenal wts (♂); ↓ Hgb, Hct and sedimentation values, ↓ pituitary and adrenal wts (♀) Depilation around the nose was observed at all dose levels which spread over the whole body. Depilation was not noted following 2 weeks recovery.
4-Week inhalation toxicity study Sprague Dawley rats PMRA # 2126786	NOAEL = 0.063 mg/L LOAEL = 0.21 mg/L Based on ↑ RBC and Hgb, ↓ sedimentation values; ↓ bwg, ↓ Hct, ↑ pituitary, adrenal and thyroid wts (♂); ↓ pituitary, adrenal, thyroid and ovarian wts (♀) No treatment-related effects were noted during the 3 week recovery period.
90-Day inhalation toxicity study Sprague Dawley rats PMRA # 1157419	NOAEL = 0.104 mg/L LOAEL = 0.291 mg/L Based on eosinophilic inclusions in the olfactory epithelial cells of the nasal turbinates. At 1.066 mg/L the following observations were also noted: clinical signs of toxicity (poorly groomed fur, dirty tails and a reduced response to a sharp knock on the chamber door), ↑ liver wts, ↓ thrombotest time; ↑ absolute kidney wts, cortical vacuolation of adrenals (♂); ↑ staining of urogenital region, ↑ ALP and eosinophils, ↑ absolute thyroid and adrenal wts, centrilobular hepatocyte enlargement and follicular thyroid cell enlargement (♀)

Study Type/Animal/PMRA #	Study Results
104-Week chronic toxicity/ carcinogenicity study B6C3F1 mice PMRA # 1210991, 1211104, 1236486, 1233957	NOAEL = 45 mg/kg bw/day LOAEL = 150 mg/kg bw/day Based on ↓ bwg, ↑ liver wts, mild hepatomegaly, clear cell foci/areas and nodular hyperplasia of the liver (♂) Increased combined incidence of hepatocellular adenomas and carcinomas in ♀ (not statistically significant) only marginally exceeded historical control range. Equivocal evidence of carcinogenicity in females
105/118-Week dietary chronic toxicity/ carcinogenicity study Fisher 344 rats PMRA # 1211105, 1211106, 1149486, 1236487	NOAEL = 47/56 mg/kg bw/day LOAEL = 141/168 mg/kg bw/day Based on ↓ ALT; ↑ relative liver wts, dilatation of sinuses in mesenteric lymph nodes and hepatocytic hypertrophy (♂); ↓ bwg and AST (♀) Increased incidence of adenomas and carcinomas of the preputial gland; however this finding was not repeated in a second study in rats at significantly greater dose levels (PMRA # 1166306, 1166307, 1166308).
104-Week chronic toxicity/ carcinogenicity study Fisher 344 rats PMRA # 1166306, 1166307, 1166308	NOAEL = 51/63 mg/kg bw/day LOAEL = 531/653 mg/kg bw/day Based on clinical signs of toxicity (hunched posture, urinary staining and a thin build), ↓ bw, bwg and fc, ↑ liver wts, ↓ absolute heart wts; ↑ ALP, ↓ LDH and urine volume (♂); ↑ platelets, LAP, ALB and A/G ratio, ↓ phospholipids, total cholesterol and fibrinogen, ↑ brain wts, panacinar hepatocytic hypertrophy, posterior capsular opacity, pale areas in the lungs (♀) Increased incidence of hepatocellular adenomas and carcinomas at the high dose in both sexes. Increased incidence of uterine adenomas and adenocarcinomas in high dose ♀. Evidence of carcinogenicity at doses greater than the MTD
2-Generation dietary reproduction toxicity study Sprague-Dawley rats PMRA # 1166309	<u>Parental Toxicity</u> NOAEL = 59/70 mg/kg bw/day LOAEL = 177/208 mg/kg bw/day Based on ↓ bwg (GD 0-20, LD 1-7), ↑ liver wts, hepatocellular hypertrophy (♀) in F_0 and ↓ bw and bwg during gestation, ↓ fc , bile duct proliferation; ↓ absolute testicular wts in F_1 <u>Reproductive Toxicity</u> NOAEL = 59/70 mg/kg bw/day LOAEL = 177/208 mg/kg bw/day Based on ↑ number of stillborn pups in F_1 <u>Offspring Toxicity</u> NOAEL not established LOAEL = 70 mg/kg bw/day Based on ↓ pup wt/litter in F_2

Study Type/Animal/PMRA #	Study Results
2-Generation dietary reproduction toxicity study Sprague-Dawley rats PMRA # 1143142, 1210990	Parental Toxicity NOAEL = 80/76 mg/kg bw/day LOAEL = 255/228 mg/kg bw/day Based on ↓ bwg; ↓ bw, ↑ liver wt, yellow pigment in uterine suspensory ligament in F_0, and ↓ bwg (♂); ↓ bw, ↑ liver and spleen wts (♀) in F_1 Reproductive Toxicity NOAEL = 80/76 mg/kg bw/day LOAEL = 255/228 mg/kg bw/day Based on ↓ number of offspring born and alive 1 day following birth (F_{1b}), slightly ↓ litter sizes and litter wts (F_{1b}), ↓ litter wts (F_{2a} and F_{2b}) Offspring Toxicity NOAEL = 80/76 mg/kg bw/day LOAEL = 255/228 mg/kg bw/day Based on ↓ number of offspring born and alive 1 day following birth (F_{1b}), slightly ↓ litter sizes and litter wts (F_{1b}), slightly ↓ litter wts (F_{2a} and F_{2b}), slightly higher incidence of small pups (F_{2b}), sinusoidal chronic inflammatory cells in the liver (after weaning), ↓ bwg (F_{2b}), ↑ relative liver wt; ↓ bw (♂)
Developmental toxicity study Sprague-Dawley rats PMRA # 1142585, 1143143, 1214826	Maternal Toxicity NOAEL = 1000 mg/kg bw/day LOAEL = 3000 mg/kg bw/day Based on ↓ bw (GD 15), bwg and fc, ↑ water intake Developmental Toxicity NOAEL = 1000 mg/kg bw/day LOAEL = 3000 mg/kg bw/day Based on ↓ fetal bw, ↑ incidence of small fetuses, slight dilation of the brain ventricles and the space between the body wall and organs (sign of immaturity), ↑ percentage of incomplete ossification of the caudal vertebrae
Range-finding developmental toxicity study New Zealand White rabbits PMRA # 1227063	No NOAEL established (range-finding) Maternal toxicity noted at ≥500 mg/kg bw/day included clinical signs of toxicity (green staining in urogenital area and ↓ defecation), ↓ bwg and fc, ↑ number of mortalities and abortions Developmental toxicity noted at ≥500 mg/kg bw/day included ↓ fetal bw and ↑ number of abortions
Developmental toxicity study New Zealand White rabbits PMRA # 1227068	Maternal Toxicity NOAEL =100 mg/kg bw/day LOAEL = 300 mg/kg bw/day Based on 1 mortality (GD 20), ↓ bwg (GD 7-19), weight loss (GD 7-10) and ↓ fc Developmental Toxicity NOAEL =300 mg/kg bw/day LOAEL = 500 mg/kg bw/day Based on umbilical herniation of the intestines and a rudimentary left atrium (1 fetus), hydrocephaly (4 fetuses from 3 separate litters)

Study Type/Animal/PMRA #	Study Results
Reverse mutation assay *Salmonella typhimurium* (TA1538 and TA1978), *Escherichia coli* (W3623 pol- and wildtype) and *Bacillus subtilis* (H17 and M45) PMRA # 2126780	Negative
Reverse mutation assay *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA1538) and *Escherichia coli* (WP-2 uvrA) PMRA # 2126773	Negative
Chromosomal aberrations Chinese hamster ovary cells (CHO-K1) PMRA # 1143144	Negative
Chromosomal aberrations Chinese hamster ovary cells (CHO-K1) PMRA # 1143145	Negative
Unscheduled DNA Synthesis Human Cells (HeLaS3) PMRA # 2126775	Negative
Chromosomal aberrations Bone marrow cells of ICR mice PMRA # 2126777	Negative
Acute range-finding neurotoxicity Study Wistar rats PMRA # 2050133	No NOAEL established (range-finding) No evidence of neurotoxicity
Acute neurotoxicity study Wistar rats PMRA # 2126795 and 2050131	NOAEL = 2,000 mg/kg bw/day (HDT) No evidence of neurotoxicity

Study Type/Animal/PMRA #	Study Results
13-Week dietary neurotoxicity study Wistar rats PMRA # 2126797 and 2050134	NOAEL = 727/230 mg/kg bw/day LOAEL (♂) = 1456 mg/kg bw/day Based on ↓ bwg and fc LOAEL (♀) = 739 mg/kg bw/day Based on ↓ bw and bwg No evidence of neurotoxicity
In vitro metabolism study various strains of animals PMRA # 2221847	Without NADPH: The guinea pig liver preparation was most active in degrading d-trans-phenothrin, followed by the dog, rabbit, rat and mouse. In all species tested, the major metabolite identified was 3-phenoxybenzyl alcohol. Smaller amounts of 3-phenoxybenzoic acid and a trace amount of 3-(4'-hydroxy) phenoxybenzoic acid were also formed. With NADPH: The percent degradation of d-trans-phenothrin was not affected by the addition of NADPH except in the dog. Addition of NADPH gave rise to a decrease in 3-phenoxybenzyl alcohol with an accompanying increase in 3-phenoxybenzoic acid and unidentified other-soluble metabolites. The formation of 3-(4'-hydroxy)phenoxybenzoic acid was not affected by NADPH.
In vivo Uterotrophic and Hershberger assays Sprague Dawley rats PMRA # 2221852	Uterotrophic assay: No treatment-related effects noted on clinical signs, body weight, food consumption, kidney or uterine weights. 1,000 mg/kg bw/day: ↑ liver wts Hershberger assay: No treatment-related effects noted, in the presence or absence of testosterone propionate, on clinical signs of toxicity, body weight, food consumption, serum androgen levels, kidney weights or on the weights of the accessory glands and/or tissues (i.e. ventral prostate, dorso-lateral prostate, seminal vesicles with coagulating glands, levator ani plus bulbocavernosus muscles, glans penis and Cowper's glands). ≥300 mg/kg bw/day: ↑ liver wts Negative.

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for d-Phenothrin

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Short- and Intermediate-term dermal	21-day dermal toxicity study – rats	NOAEL = 1,000 mg/kg bw/day (HDT)	100
Non-dietary oral ingestion	Oral (gavage) developmental toxicity study - rabbits	NOAEL = 100 mg/kg bw/day (weight loss, ↓ body weight gain and food consumption)	100
Cancer	Not required		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.

Table 4 Toxic Substances Management Policy Considerations–Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	9 days
	Water	Half-life ≥ 182 days	Not available
	Sediment	Half-life ≥ 365 days	Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Not available EPISuite OH half-life 0.101 days
Bioaccumulation[4]	Log K_{OW} ≥ 5		>6*
	BCF ≥ 5000		EPISuite 338 (upper trophic)
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

1 All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e. all other TSMP criteria are met).

2 The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

3 If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

4 Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

* While the log Kow is high, studies showed that 94-100% of the product was excreted by rats through feces and urine in seven days.

Table 5 Alternatives Currently Registered in Canada for Use on Dogs to Kill Fleas, Ticks and/or Mosquitoes.

Mode of Action Group	Active Ingredient		
	Fleas	Ticks	Mosquitoes
1A: Carbamates	Carbaryl Propoxur	Carbaryl Propoxur	
1B: Organophosphates	Tetrachlorvinphos	Tetrachlorvinphos	
3A: Pyrethroids, Pyrethrins	D-trans allethrin Permethrin Pyrethrins Resmethrin	D-trans allethrin Permethrin Pyrethrins Resmethrin	Permethrin Pyrethrins

Mode of Action Group	Active Ingredient		
	Fleas	Ticks	Mosquitoes
4A: Neonicotinoids	Imidacloprid	Imidacloprid	
7A: Juvenile Hormone Mimics - Analogues	S-Methoprene		
7C: Juvenile Hormone Mimics - Other	Pyriproxyfen		
19: Octopaminergic Receptor Agonists		Amitraz	
21: Mitochondrial Complex I Electron Transport Inhibitors - Other	Rotenone		
Other:	Potassium Salts of Fatty Acids	Potassium Salts of Fatty Acids	

Table 6 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

a) Acceptable Use Claims

Acceptable Pest Claim	Proposed and Acceptable Use Pattern			
	Amount of product in tube (ml)	Size of dog (kg)	Minimum Age of Animal	Re-application interval
Kills Fleas and Ticks for up to 30 days on dogs and puppies Reduces Biting by Mosquitoes for up to 30 days on dogs and puppies	0.65	2.5 to 6	12 weeks	Monthly
	1.3	6 to 14	12 weeks	Monthly
	4.1	14 to 28	12 weeks	Monthly
	5.9	Over 28	12 weeks	Monthly

b) Unsupported Use Claims

The following claim was not supported due to insufficient value information:

- Repels Fleas and Ticks for up to 30 days on dogs and puppies

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
1874106	2010, DACO 3.5.4 & 3.5.5, DACO: 3.5.4,3.5.5 CBI
1874108	2010, Interim Stability Report, DACO: 3.5.10 CBI
1874109	1999, Product Chemistry Data Requirements, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 3.4.2, 3.5.1, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.3, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
1874110	2010, DACO 3, DACO: 3.1.1, 3.1.2, 3.1.3, 3.1.4 CBI
2042411	2011, End-Use Product Manufacturing Process, DACO: 3.2.2 CBI
2042598	2011, Validation of Test Method [CBI Removed] Determination of S-Methoprene and/or Sumitherin in One Spot by HPLC, DACO: 3.4.1 CBI
2042599	2008, GLP Stability Report for Hartz 4-in-l Flea and Tick Drops for Dogs, DACO: 3.5.10 CBI
2042600	2011, Application to Register Hartz Reference 118 End-Use Product, DACO: 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.3, 3.5.7, 3.5.8, 3.5.9 CBI
2065316	2011, DACO: 3.5.7 pH, DACO: 3.5.7 CBI
2097940	2009, Determination of S-Methoprene and/or Sumithrin in Topical Drops by [CBI Removed], DACO: 3.4.1 CBI
2097941	2011, Hartz ULTRA GUARD Plus Flea and Tick Drops for Dogs Determining Product Chemistry Data, DACO: 3.5.11, 3.5.6, 3.5.7, 3.5.9 CBI
2097942	2011, Summary of the Physical/Chemical Properties (PR Notice 98-1), DACO: 3.5.11, 3.5.6, 3.5.7, 3.5.9 CBI
2097943	2011, Storage Stability and Corrosion Characteristics, DACO: 3.5.10, 3.5.14 CBI
2097944	2003, Alternate Names, DACO: 3.5.10, 3.5.14 CBI
2097945	2002, CSF, DACO: 3.5.10,3.5.14 CBI
2107330	2011, Hartz UltraGuard Plus Flea and Tick Drops for Dogs Product Chemistry, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 3.4.2, 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.2, 3.5.3, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
2065311	2011, DACO: 3.5.7 pH, DACO: 3.5.7 CBI

2097939	2011, DACO: 3.2.2 Title: Description of the Formulation Process, DACO: 3.2.2 CBI
2065327	2011, DACO: 3.5.7 pH, DACO: 3.5.7 CBI
2042595	2011, END-USE PRODUCT MANUFACTURING PROCESS, DACO: 3.2.2 CBI
2065038	2011, DACO: 3.5.7 pH, DACO: 3.5.7 CBI
2065052	2011, DACO: 3.5.7 pH, DACO: 3.5.7 CBI
2065071	2011, DACO: 3.5.7 pH, DACO: 3.5.7 CBI
2065276	2011, DACO: 3.5.7 pH, DACO: 3.5.7 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
2222322	1987, Acute oral toxicity of S-2539F in rats, DACO 4.2.1
1157417	1987, Acute dermal toxicity of S-2539F in rats, DACO 4.2.2
2126786	1975, Acute & subacute inhalation of S-2539 and S-2539 Forte in mice and rats, DACO 4.3.7
2126819	1995, An acute (4-hour) inhalation toxicity study of Sumithrin in the rat via whole-body exposure, DACO 4.2.3
1142183	1988, Primary eye and skin irritation tests with Sumithrin in rabbits, DACOs 4.2.4 and 4.2.5
1142184	1988, Skin sensitization test with Sumithrin in guinea pigs, DACO 4.2.6
1233959	1983, Sumithrin: five week range-finding toxicity study in mice, DACO 4.3.1
1142584	1991, Sumithrin: Toxicity in dietary administration to rats over 13 weeks, Addendum to Final Report, DACO 4.3.1
1233961	1983, Sumithrin: Toxicity in dietary administration over 13 weeks in rats, DACO 4.3.1
1143141	1990, Comments on the six month oral toxicity study of S-2539 Forte (Sumithrin) in rats, DACO 4.3.1
1227040	1989, Five-day oral toxicity study in female rabbits with Sumithrin, DACO 4.3.1
2126801, 2126802, 2126804, 2126806	1981, Subchronic toxicity study in dogs, DACO 4.3.2
1216240	1987, Chronic toxicity study in dogs with Sumithrin T.G., DACO 4.4.1
1157418	1989, Final Report 21-day dermal toxicity study in rats with Sumithrin T.G., DACO 4.3.4
1157419	1989, Sumithrin T.G. 90-day inhalation toxicity study in the rat, DACO 4.3.6

1210991, 1211104, 1236486, 1233957	1987, Sumithrin: Oncogenicity and toxicity study in mice, DACOs 4.4.1 and 4.4.2
1211105, 1211106, 1236487	1987, Sumithrin: Combined toxicity and oncogenicity study in rats, DACOs 4.4.1 and 4.4.2
1149486	1993, Sumithrin: Combined toxicity and oncogenicity study in rats, Addendum to Final Report Second Addendum to 85/SUM003/0586, DACO 4.4.2
1166306, 1166307, 1166308	1995, Final Report: Sumithrin combined oncogenicity and toxicity study by dietary administration to F-344 rats for 104 weeks, DACO 4.4.4
1166309	1995, Final Report: Reproductive effects of Sumithrin administered orally via the diet to Crl:CD VAF/Plus rats for two generations, DACO 4.5.1
1210990	1986, Sumithrin: Effects upon reproduction performance of rats treated continuously throughout two successive generations, DACO 4.5.1
1143142	1990, Sumithrin: Effects upon reproduction performance of rats treated continuously throughout two successive generations, First Amendment to 85/SUM009/331, DACO 4.5.1
1143143, 1214826	1983, Sumithrin: Effects of oral administration upon pregnancy in the rat, DACO 4.5.2
1142585	1991, Sumithrin: Effects of oral administration upon pregnancy in the rat, Addendum to Final Report, DACO 4.5.2
1227063	1989, A range-finding teratology study in rabbits with Sumithrin, DACO 4.5.2
1227068	1989, A teratology study in rabbits with Sumithrin, DACO 4.5.2
2126780	1975, Mutagenicity of some synthetic pyrethroids, bacterial test systems, DACO 4.5.8
2126773	1981, Gene mutation test of Sumithrin in bacterial system, DACO 4.5.4
1143144	1987, Sumithrin: In vitro chromosomal aberration test of S-2539F in Chinese Hamster Ovary cells, DACO 4.5.4
1143145	1989, An in vitro cytogenetic assay measuring chromosomal aberration frequencies in Chinese Hamster Ovary cells with Sumithrin, DACO 4.5.4
2126775	1984, Unscheduled DNA synthesis in Human cells cell line: HeLa S3, DACO 4.5.8
2126777	1981, In vivo chromosomal aberration test of Sumithrin on bone marrow cells of mice, DACO 4.5.7
2050133	2008, Acute oral peak effect study in rat, DACO 4.5.12
2126795, 2050131	2008, Acute oral neurotoxicity (gavage) study in rats, DACO 4.5.12
2126797, 2050134	2010, 13-week oral neurotoxicity (feeding) study in rats, DACO 4.5.13
1874099	1999, Dermal Sensitization Study in Guinea Pigs (Buehler Method), DACO: 4.6.6
1874100	1999, Primary Skin Irritation Study in Rabbits, DACO: 4.6.5
1874101	1999, Primary Eye Irritation Study in Rabbits, DACO: 4.6.4
1874102	2010, DACO 4.6.3 Acute Inhalation Waiver, DACO: 4.6.3
1874103	1999, Acute Dermal Toxicity Study in Rabbits - Limit Test, DACO: 4.6.2

1874104	1999, Acute Oral Toxicity Study in Rats - Limit Test, DACO: 4.6.1
1874090	1999, Domestic Animal Safety Study of a Monthly Stripe-On Formula in Adult Beagles, DACO: 4.9
1874092	1999, Tolerance of a Monthly Stripe-On Formula Containing Adulticide and IGR in Pups, DACO: 4.9

3.0 Value

PMRA Document Number	Reference
1874111	2009, A Study to Measure the Efficacy of an Adulticide/IGR Product Against Flea Egg Hatch and Adult Fleas and Ticks on Dogs, DACO: 10.2.3.3
1874112	2009, A Study to Measure the Efficacy of an Adulticide/IGR Product Against Flea Egg Hatch and Adult Fleas and Ticks on Dogs, DACO: 10.2.3.3
1874113	1999, A Study to Evaluate the Repellent Activity of an Adulticide/IGR Product Against Adult Ticks and Fleas on Dogs, DACO: 10.2.3.3
1874114	2009, Efficacy Studies - Summaries, DACO: 10.2.3.1
1874115	2010, 10.2.1: Mode of Action and 10.2.2: Description of Pest Problem, DACO: 10.2.1, 10.2.2
1874116	2010, Efficacy Summary, DACO: 10.1
2042583	1999, A Study to Evaluate the Repellent Activity of an Adulticide/IGR Product Against Adult Ticks and Fleas on Dogs, DACO: 10.2.3.2(C)
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B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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